REMARKS

Claims 1-22 are pending. Claims 6, 9 and 15-17 stand withdrawn as being directed to a non-elected invention. Accordingly, claims 1-5, 7, 8, 10-14 and 18-22 are under examination. Claims 1 and 19 have been amended. Support for the amendments can be found throughout the application as filed. Support for the amendment to step 1 can be found in the preamble of each claim, respectively. Support for the amendment directed to a suitably programmed computer can be found at, for example, 0044. Support for the amendment directed to simultaneously solving the linear optimization problem to provide an optimal solution can be found at, for example, paragraphs 0020 and 0038-0043. Accordingly, the amendments do not introduce new matter and entry thereof is respectfully requested.

Applicants acknowledge the withdrawal of the various grounds of rejection under 35 U.S.C. § 103. In particular, rejection of claims 1, 5, 7, 8, 10, 11, 13, 14, 19 and 20 as allegedly obvious over Hatzimanikatis et al., *AIChE J.* 42:1277-1292 (1996), in view of Bhaskar et al., *Rev. Chem. Eng.* 16:1-54 (2000); rejection of claims 1, 2, 4 and 18 as allegedly obvious over Hatzimanikatis et al., *supra*, in view of Bhaskar et al., *supra*, and further in view of Yang et al., *Metabolic Engineering* 1:26-34 (1999); rejection of claims 1, 5, 7, 8, 10-14, 19 and 20 as allegedly obvious over Burgard et al., *Biotechnol. Bioeng.* 74:364-375 (2001), in view of Bhaskar et al., *supra.*, and rejection of claims 1-4 and 18 stand as allegedly obvious over Burgard et al., *supra*, in view of Bhaskar et al., *supra*, and further in view of Yang et al., *supra.* have been withdrawn.

Rejections Under 35 U.S.C. § 101

Claims 1, 3-5, 7, 8, 10-14 and 18-22 stand rejected under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter. The Examiner alleges that the claims are directed to an abstract idea and that they do not meet the machine-or-transformation test allegedly because the claims do not recite an electronic transformation nor do they require a particular machine.

Claims 1 and 19 are directed to a method for determining candidates for gene deletions using a computer model of a metabolic network associated with an organism. The model includes a plurality of metabolic reactions defining metabolite relationships. The method includes solving a linear optimization problem of objective functions of the plurality of

metabolic reactions and providing a visual output of at least one candidate gene deletion to a user.

In re Bilski, 545 F.3d 943, (Fed. Cir. 2008) held that a process claim defines patentable subject matter if "(1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article to a different state or thing." *Id.* at 954, 956 (*citing Gottschalk v. Benson*, 409 U.S. 63, 70 (1972)). Applicants respectfully submit that the claimed method meets either or both branches of this "machine-or-transformation" test articulated by the *Bilski* court.

Amended claims 1 and 19 expressly recite that the methods are performed in a computer. Both claims require providing a computer model having an electronic representation of a plurality of metabolic reactions and executing commands in a suitably programmed computer using the stored data structure. These elements clearly tie the claimed method to a particular machine or apparatus, namely a suitably programmed computer (*see also*, Interim Patent Subject Matter Eligibility Examination Instructions, August 24, 2009, at page 6, para. 2, "the general purpose computer may be sufficiently "particular" when programmed to perform the process steps ... because a general purpose computer, in effect, becomes a special purpose computer once it is programmed to perform particular functions"). Accordingly, claims 1, 19 and their dependents satisfy the machine-or-transformation test because the method for predicting a *Saccharomyces cerevisiae* physiological function is implemented by a particular machine.

Although not required to satisfy both alternatives of the machine-or-transformation test, independent claims 1 and 19 of the subject invention nevertheless also satisfies the alternative transformation branch of the test.

In re Bilski, 545 F.3d 943, 959-60 (Fed. Cir. 2008) held that the claimed method was not directed patent-eligible subject matter because there was no transformation of an article into a different state or thing. In arriving at this conclusion, the court recognized that "[t]he raw materials of many information-age processes ... are electronic signals and electronically manipulated data" and concluded:

> So long as the claimed process is limited to a practical application of a fundamental principle to transform specific data, and the claim is limited to a visual depiction that represents specific physical objects or substances, there is no danger that the scope of the claim would wholly pre-empt all uses of the principle.

Id. at 963 (emphasis added).

Bilski further clarified that electronic transformation of data is sufficient to render a process claim patent eligible subject matter when the court stated:

> We further note for clarity that the electronic transformation of the data itself into a visual depiction in *Abele* was sufficient; the claim was not required to involve any transformation of the underlying physical object that the data represented. We believe this is faithful to the concern the Supreme Court articulated as the basis for the machine-or-transformation test, namely the prevention of pre-emption of fundamental principles.

Id. at 963 (emphasis added).

Thus, *Bilski* found that, when applied to electronic signals and electronically manipulated data, the transformation branch of the machine-or-transformation test does not require transformation of an underlying physical object the data may represent. Rather, the transformation branch is satisfied when electronic data is transformed into a visual depiction. Applicants respectfully point out that the methods of claims 1 and 19 satisfy this branch of the test. Both claims 1 and 19 employ a computer model of an electronic representation of a plurality of metabolic reactions and provide a visual output of the at least one candidate gene deletion to a user.

Applicants further point out, although not required, that the underlying objects represented by the data in the claimed computer model used on the claimed methods correspond to physical objects or substances in biochemical reaction networks within a living cell. For example, the data represents enzymes, substrates, products and co-factors and is electronically represented in a computer. Computational methods disclosed in the specification are applied to the claimed electronic representation to determine the at least one candidate gene deletion and the results are visually displayed. Hence, the claimed invention represents underlying physical components of a living cell in electronic data, manipulates that electronic data to generate a representation of the physical components predictive of a physiological function and transforms that representation to a visual output. Therefore, the claim "transforms specific data . . . to a visual depiction that represents specific physical objects or substances [and] there is no danger that the scope of the claim would wholly pre-empt all uses of the principle. *Bilski*, 545 F.3d at 963 (*supra*). Accordingly, claims 1 and 19 are patent-eligible subject matter because they also satisfy the transformation branch of the machine-or-transformation test articulated by the

Supreme Court and clarified in *Bilski*. Applicants respectfully request that this ground of rejection be withdrawn.

In light of the above remarks and amendments, Applicants submit that the claimed invention falls within statutory patentable subject matter and respectfully request withdrawal of this ground of rejection.

Rejections Under 35 U.S.C. § 103

Claims 1, 5, 7, 8, 10, 11, 13, 14 and 19-22 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis et al., *AIChE J.* 42:1277-1292 (1996), in view of Varma et al., *Biotechnol. and Bioeng.* 42:59-73 (1993) and in view of Bhaskar et al., *Rev. Chem. Eng.* 16:1-54 (2000). Hatzimanikatis et al. is cited for allegedly describing that objective functions can be formed for any process of interest, but is conceded by the Examiner to not describe coupling of cellular and bioengineering objective functions in a single optimization problem. The Examiner alleges that Varma et al. describe the coupling of cellular and bioengineering objective functions and that Bhaskar et al. provides an expectation of success allegedly because real-world chemical engineering problems require the simultaneous optimization of several objectives that cannot be combined into a single, meaningful scalar objective function. Hatzimanikatis et al is cited for allegedly describing that the examination of different regulatory structures indicates that amino acid selectivity can be improved while maintaining constant growth and Varma et al. allegedly describes that the balance between growth and biochemical production is important for successful bioprocess. Applicants respectfully submit that the claimed methods are unobvious over the combination of Hatzimanikatis et al., Varma et al. and Bhaskar et al.

When determining whether a claim is obvious, an examiner must make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). Moreover, as the Supreme Court recently stated, "*there must be some articulated reasoning* with some rational underpinning to support the legal conclusion of obviousness." *KSR*

Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (emphasis added)).

Applicants respectfully point out that the cited combination of references or general knowledge in the art fail to suggest or provide an incentive to one skilled in the art to arrive at the claimed invention with a reasonable expectation of success. The claimed invention employs a linear optimization problem to arrive at an optimal solution that couples, or simultaneously solves for, at least one cellular objective function with at least once bioengineering objective function. Other than having similar terms in the references, there is nothing in the cited combination that would lead one skilled in the art to arrive at such a coupling using a linear optimization problem.

As pointed out previously, Hatzimanikatis et al. fail to suggest coupling a cellular objective function with a bioengineering objective function and solving for an optimal solution using linear programming. Rather, Hatzimanikatis et al. describe solutions to different linear optimization problems. Similarly, neither do Varma et al. or Bhaskar et al. provide any suggestion or incentive for coupling a cellular objective with a bioengineering objective and simultaneously solving for an optimal solution using linear programming. Applicants respectfully submit that such a suggestion is missing.

The Examiner alleges that Varma et al. describe the coupling of cellular and bioengineering objective functions and describe that the balance between growth (cellular objective) and biochemical production (bioengineering objective) is important for a successful bioprocess. With respect to the latter point, as Applicants previously stated of record, the conclusion that growth and metabolite production are related in an organism has long been established. In contrast, coupling a cellular objective function with a bioengineering function in a metabolic model using a linear optimization problem has not. The passages cited by the Examiner for allegedly describing the coupling of two objective functions is unsupported. As described further below, the passage at page 67 describes separate optimization of different objective functions while the passage at page 60 describes the use of shadow prices for the separate optimization. Further, Applicants have not found where in Varma et al. such a suggestion exists. Rather, Varma et al. describe:

> We have determined the production capabilities of the *E. coli* metabolic network by incorporating a drain for specific biochemicals in the metabolic network and maximizing them using linear programming. We compute maximal yields of amino acids and nucleotides from three substrates: glucose, glycerol, and acetate.

Id. at page 64, col. 2, first paragraph (emphasis added).

Thus, Varma et al. does no more than solve for a single objective function, maximal yields of amino acids, on each of three different substrates. Each optimization problem is performed separately from the others. This conclusion is further illustrated when Varma et al. describe:

> An optimal trade-off between growth and biochemical production can be assessed by choosing a production rate for a particular product between zero and the maximum production rate and then maximizing the growth rate.

Id. at page 67, col. 2, second paragraph (emphasis added).

Thus, a set value (between zero and maximum rate) is chosen for one function and the second function is optimized separately. There is no coupling of cellular and bioengineering objective functions to simultaneously solve for an optimal solution. Accordingly, Varma et al. is cumulative with Hatzimanikatis et al. and fails to suggest coupling two different objective functions using linear optimization. Rather, Varma et al. describe choosing a set value for one function and then optimizing the other function.

As previously pointed out with respect to Bhaskar et al., this reference similarly fails to suggest or provide any incentive for one skilled to couple divergent objective functions such as cellular and bioengineering objective functions using a linear optimization problem to yield an optimal solution. Bhaskar et al. is a review of multiobjective optimization in chemical engineering and describe various methods for generating Pareto sets. These methods include, for example, the lexicographic approach, Parametric approach, ε-Constraint approach and Goal Programming, none of which employ a linear optimization problem that can achieve an optimal solution because these methods either: 1) arbitrarily assign weights to multiple objective functions prior to solution (parametric), 2) arbitrarily set constraints on secondary objective functions prior to solution (e-constraints), or 3) arbitrarily set goals for multiple objective functions prior to solution that the optimization algorithm tries to match (goal programming).

In this regard, for example, the lexicographical approach requires a hierarchical solution procedure (i.e., not solution of a single linear problem, but many; *see e.g.*, pages 11-12). However, the claimed invention solves one linear optimization problem. The parametric approach solves an optimization problem with objective functions being given different weights prior to solution. As Bhaskar et al. point out at, for example, pages 13-14, *a priori* knowledge of the weights is practically not possible. The claimed method does not require weighting of the objective functions and can achieve an optimal solution. The e-constraints approach involves solution of a linear programming problem that maximizes or minimizes a single objective function subject to constraints on the other objective functions (see, for example, pages 14-21). In contrast, the claimed method solves for both the cellular objective and bioengineering objective at the same time. The Goal Programming approach requires one to set 'targets' for the different objective functions prior to solution. The claimed method does not require arbitrary goals and can achieve an optimal solution.

Further, for example, the modified ε-constraint approach described beginning on page 18, last paragraph, generally illustrates the various approaches described in Bhaskar et al. for multiobjective optimization. Bhaskar describes an "interactive, iterative optimization procedure, based on the solution of the non linear programming (NLP) problems was used to obtain the preferred solution for the two cases" (page 19, lines 10-12; *see also* page 20, line 6). Thus, the methods reviewed by Bhaskar et al. employ the approach of selecting and fixing a Pareto optimal set corresponding to one objective function while stepwise maximizing the other Pareto set to find a solution. The process is iterated until solutions are identified for both Pareto sets. Accordingly, there is no coupling and solving for the different objective functions together. Further, as pointed out above, any step-wise solution to solving multiobjective optimization employed non-linear programming problems. Employing a linear programming problem to simultaneously solve multiple Pareto optimal sets was computationally intractable (see, for example, subject application at paragraph 0038-0043). On the other hand, non-linear methods such as those described in Bhaskar et al. could find solutions, but were not likely to yield the optimal solution (see, for example, Bhaskar et al. at page 6, first para.). Thus, the use of a linear programming problem that couples divergent objective functions as claimed was unexpected and was neither suggested in the cited combination of references. Further, there is nothing in the

cited art that would suggest that one skilled in the art could have arrived at the claimed invention using general knowledge in the art.

Thus, Hatzimanikatis et al. and Varma et al. independently solve different linear optimization problems, but fail to provide any suggestion or incentive for coupling cellular and bioengineering objectives using a linear optimization problem. Bhaskar et al. employs non-linear programming problems and fail to suggest using a linear optimization problem for simultaneously solving for different objectives to arrive at an optimal solution. Absent some suggestion for simultaneously solving a linear optimization problem that couples at least one cellular objective function with at least one bioengineering objective function, the cited combination cannot render the invention as claimed obvious. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claims 1, 2, 4 and 18 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Hatzimanikatis et al., *AIChE J.* 42:1277-1292 (1996), in view of Varma et al., *Biotechnol. and Bioeng.* 42:59-73 (1993) and in view of Bhaskar et al., *Rev. Chem. Eng.* 16:1-54 (2000), and further in view of Yang et al., *Metabolic Engineering* 1:26-34 (1999). Hatzimannikatis et al., Varma et al. and Bhaskar et al. are cited as applied to claims 1, 5, 7, 8, 10, 11, 13, 14 and 19-22 above. Yang et al. is cited for allegedly describing use of a candidate gene to genetically modify an organism. Applicants respectfully submit that the claimed methods are unobvious over the combination of Hatzimanikatis et al., Varma et al., Bhaskar et al. and Yang et al.

As set forth above, Applicants respectfully submit that Hatzimanikatis et al. in combination with Varma et al. and Bhaskar et al. do not teach or suggest the claimed methods. Furthermore, Applicants respectfully submit that Yang et al. does not cure the deficiencies of the combination of Hatzimanikatis et al., Varma et al. and Bhaskar et al. Yang et al., at best, describe the use of metabolic flux analysis in an *Escherichia coli* strain deficient in the acetate production pathway. However, as discussed previously on the record, Yang et al. does not describe forming a linear optimization problem that couples at least one cellular objective function with a bioengineering objective function and solving that linear optimization problem to provide an optimal solution. Accordingly, Applicants respectfully submit that the claimed methods are unobvious over Hatzimanikatis et al., in combination with Varma et al., Bhaskar et al. and Yang et al. Therefore, Applicants respectfully request that this rejection be withdrawn.

Claims 1, 5, 7, 8, 10-14 and 19-22 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Burgard et al., *Biotechnol. Bioeng.* 74:364-375 (2001), in view of Varma et al., *Biotechnol. and Bioeng.* 42:59-73 (1993) and in view of Bhaskar et al., *Rev. Chem. Eng.* 16:1-54 (2000). As conceded by the Examiner, Burgard et al. do not teach the generation of a bilevel optimization problem or the coupling of cellular and bioengineering objective functions. Varma et al. is alleged to describe coupling of cellular and bioengineering objective functions while Bhaskar et al. allegedly describes that real-world chemical engineering problems require the simultaneous optimization of several objectives that cannot be combined into a single, meaningful scalar objective function. Applicants respectfully submit that the claimed methods are unobvious over the combination of Burgard et al., Varma et al. and Bhaskar et al.

As described previously of record and acknowledged by the Examiner, Burgard et al. do not describe forming a linear optimization problem that couples a cellular objective function and a bioengineering objective function and simultaneously solving that linear optimization problem to obtain an optimal solution as claimed. Similarly, as set forth above, Varma et al. also fails to suggest forming such a linear optimization problem that couples cellular and bioengineering objective functions and solving it for an optimal solution. Rather, Varma et al. chooses a fixed value for one objective and separately, and iteratively, solves for the second value. Bhaskar et al. describe numerous multiobjective optimization methods, but none of which employ a linear optimization problem to couple two diverse objective functions. Absent some suggestion for simultaneously solving a linear optimization problem that couples at least one cellular objective function with at least one bioengineering objective function, the cited combination cannot render the invention as claimed obvious. Accordingly, withdrawal of this ground of rejection is respectfully requested.

Claims 1-4 and 18 stand rejected under 35 U.S.C. § 103 as allegedly obvious over Burgard et al., *Biotechnol. Bioeng.* 74:364-375 (2001), in view of Varma et al., *Biotechnol. and Bioeng.* 42:59-73 (1993) and in view of Bhaskar et al., *Rev. Chem. Eng.* 16:1-54 (2000), and further in view of Yang et al., *Metabolic Engineering* 1:26-34 (1999). Burgard et al., Varma et al. and Bhaskar et al. are cited as applied to claims 1, 5, 7, 8, 10-14 and 19-22 above. Yang et al. is cited for allegedly describing use of a candidate gene to genetically modify an organism.

Applicants respectfully submit that the claimed methods are unobvious over the combination of Burgard et al., Varma et al., Bhaskar et al. and Yang et al.

As set forth above, Applicants respectfully submit that Burgard et al. in combination with Varma et al. and Bhaskar et al. do not teach or suggest the claimed methods. Furthermore, Applicants respectfully submit that Yang et al. does not cure the deficiencies of the combination of Burgard et al., Varma et al. and Bhaskar et al. Yang et al., at best, describe the use of metabolic flux analysis in an *Escherichia coli* strain deficient in the acetate production pathway. However, as discussed previously on the record, Yang et al. does not describe forming a linear optimization problem that couples at least one cellular objective function with a bioengineering objective function and solving that linear optimization problem to provide an optimal solution. Accordingly, Applicants respectfully submit that the claimed methods are unobvious over Burgard et al., in combination with Varma et al., Bhaskar et al. and Yang et al. Therefore, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

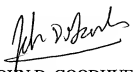
In light of the Amendments and Remarks herein, Applicant submits that the claims are in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he is invited to call the undersigned attorney.

This is a request to extend the period for filing a response in the above-identified application for three months from January 28, 2010 to April 28, 2010. Applicant is a small entity; therefore, please charge Deposit Account number 26-0084 in the amount of $555.00 to cover the cost of the three month extension.

No other fees or extensions of time are believed to be due in connection with this amendment; however, consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Reconsideration and allowance is respectfully requested.

Respectfully submitted,



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